REMARKS

The Office Action dated May 25, 2001 has been carefully reviewed and the forgoing amendments are made in response thereto. In view of these amendments and the following remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Claims 1-20 and 22-23 are pending for consideration

Summary of the Office Action

1. Applicants' amendment dated February 26, 2001 (Paper No. 7) was entered, resulting in the cancellation of claim 21.

2. Applicants remarks directed to the rejection of claim 21 under 35 U.S.C 112 (second paragraph) was withdrawn in light of the cancellation of claim 21.

3. The rejection of claim 4 under 35 U.S.C. 112 (second paragraph) as vague and indefinite for recitation of the term "sufficient time" was maintained.

4. The rejection of claims 20-23 under 35 U.S.C. 112 (first paragraph) was maintained in the absence of deposit information for the antibodies and hybridoma in these claims.

5. The rejection of claims 1-8 and 16-17 under 35 U.S.C. 102(b) as being anticipated by McDonald *et al.* (1995) Parisitology 110, 295-298 was maintained.

6. The rejection of claims 9-15 and 18-19 under 35 U.S.C. 103(a) as being unpatentable over McDonald *et al.* (1995) Parisitology 110, 295-298 in view of Riggs *et al.* (1994) Infection & Immunity 62, 1927-1939 was maintained.

Response to the Office Action

Applicants bring to the attention of the Examiner that the present invention is based on the surprising finding that to produce IgG1 class antibodies against oocyst wall antigens it is necessary to purify oocyst wall antigens from sporozoite components. This is believed to be because the sporozoite antigens are immunodominant and are therefore believed to inhibit the production of IgG1 class antibodies against the oocyst wall antigens if both sporozoite and oocyst wall antigens are co-administered to an animal. Furthermore, the present invention

provides for the first time IgG1 class antibodies reactive with oocyst wall antigens not disclosed in the cited references.

Rejections under 35 U.S.C. 112 (second paragraph)

Applicants have amended claims 4-5 to remove the term "sufficient time" in response to the rejection in the Office Action. The amended claims now define excystation parameters set forth in the specification on page 7, lines 7-16. In light of these amendments, Applicants respectfully submit that the rejection is moot and request that it be withdrawn.

Applicants are in the process of complying with the deposit requirement set forth in the Office Action and have been advised that deposit information will be available within the next month. Applicants will be supplying this deposit information in a supplemental amendment and respectfully request that the Examiner hold the rejection in abeyance until such time that the deposit information is available for submission to the Patent Office.

Rejection under 35 U.S.C. 102(b)

The rejection of claims 1-8 and 16-17 for lack of novelty based on McDonald *et al.* (1995) was maintained. Applicants respectfully submit that the Office Action has misconstrued the teachings of McDonald *et al.* (1995). The only reference to the production of monoclonal antibodies in this cited reference is in the section entitled "Monoclonal Antibodies" in the Materials and Methods section (see page 260, column 2, line 8). The method used to obtain the monoclonal antibodies is actually that of McDonald *et al.* (1991) Parasite Immunology 13, 251-259 (copy attached). Thus, the referenced method for producing monoclonal antibodies is in no way related to the section on page 260 of McDonald *et al.* (1995) which refers to the purification of oocysts which are then subsequently used to infect animals, and not to produce monoclonal antibodies.

Further, it is clear from the McDonald *et al.* (1991) that the BALB/c mice used to produce the monclonal antibodies used were immunized with oocyst homogenates and not purified oocyst antigens (see page 253, "Monoclonal Antibodies" section). Applicants emphasize that the section of McDonald *et al.* (1995) that refers to methods of purifying *Cryptosporidium* oocysts

has no relationship whatsoever to section in the same reference which deals with the production of monoclonal antibodies using methods previously described in McDonald *et al.* (1991) using oocysts homogenates.

In addition, the oocyst purification method described in McDonald *et al.* (1995) does not result in disruption of oocyst integrity nor a separation of the oocysts from oocyst antigens as is required in steps (a) and (b) of claim 1. This is because the purified oocysts are then used to infect mice (page 260, column 2, last paragraph) and therefore need to be viable and accordingly, contain viable sporozoites. The monoclonal antibodies described in McDonald *et al.* (1995) do not result from the injection of the purified oocysts into the mice. Instead, monoclonal antibodies produced by an entirely separate procedure are used to detect by immunogold electron microscopy oocysts/sporozoites present in samples of the ileum and caecum removed from animals infected with the purified oocysts.

Accordingly, McDonald *et al.* (1995) does not teach at least step (c) of the method of claim 1 because the resulting material from the oocyst treatment step described in this reference, which is injected into the mice, is purified viable oocysts and not a separated surface layer of oocysts antigens as is required by step (c). Applicants therefore submit that method claims 1 to 8 are novel over McDonald *et al.* (1995) and respectfully request that the rejection be withdrawn.

With respect to claims 16 and 17, the Office Action has provided no evidence to show that McDonald *et al.* (1995) provides a clear and unambiguous disclosure of IgG1 class monoclonal antibodies. As discussed above, the oocyst purification step is used to produce purified viable oocysts that are then injected into mice whereas the monoclonal antibody production is conducted by entirely different means. Consequently, the comment in the Office Action that McDonald *et al.* (1995) discloses that the oocysts were treated with sodium hypochlorite in the "Parasites section" is not relevant to the production of monoclonal antibodies and cannot be used to support the inherency argument set forth in the Office Action based on the assertion that acceptable methodology has been taught for making the IgG1 antibody.

Applicants also bring to the attention of the Examiner that McDonald *et al.* (1995) discloses only three monoclonal antibodies. Two are IgM antibodies (1B5 and 2B2). The other is an IgG class antibody (2C3) (see page 260, column 1 lines 13-15). Not only is there no

teaching that the sole IgG antibody is of the IgG1 class, but also, as is clear from Figure 1, antibody 2C3 reacts only with the whole sporozoite and not the oocyst surface. Accordingly, there is no disclosure in McDonald *et al.* (1995) of an IgG1 class antibody which reacts with the oocyst surface as set forth in claim 1 and respectfully submit that the rejection to claims 16 and 17 be withdrawn.

Rejections under 35 U.S.C. 103(a)

The rejection of claims 9-15 and 18-19 under 35 U.S.C. 103(a) as being unpatentable over McDonald *et al.* (1995) in view of Riggs *et al.* (1994) was maintained. Applicants respectfully submit that the misinterpretation of McDonald *et al.* (1995) in the Office Action as discussed above renders the obviousness rejection moot. In addition, Applicants further submit that the Office Action has also misconstrued Riggs *et al.* (1994) further rendering the rejection moot.

The Office Action also appears to have incorrectly combined the discussion in Riggs *et al.* (1994) (page 1928, column 1, second paragraph), which teaches the preparation of purified sporozoites, with the later discussion in the same reference that discloses immunizing cows with purified sonicated oocysts (page 1928, column 1, last paragraph). The process outlined on page 1928, column 1, second paragraph is concerned with obtaining purified sporozoites (which are contained within oocysts) and not oocysts nor oocysts surface antigens.

> "Immediately prior to excystation to obtain sporozoites....Sporozoites were isolated by DEAE-cellulose ion-exchange chromatography" [emphasis added].

Any residual oocyst material was not used further as an antigenic preparation. Furthermore, the purified oocysts referred to on page 1928, column 1, last paragraph are oocysts that have simply been isolated from calf feces by sieving and sucrose density gradient centrifugation as described in the earlier part of second paragraph, which is a standard procedure. These oocysts are intact and contain sporozoites. Therefore no separation of the oocysts from the sporozoites had taken place.

Riggs *et al.* (1994) therefore only teaches the injection of cows with (1) purified and sonicated sporozoites, (2) purified sonicated whole oocysts and (3) adjuvant only. There is no

mention anywhere in this reference of the treatment of oocysts to remove surface antigens, the separation of the surface antigens from the rest of the oocysts and subsequent injection of the surface antigen preparation into the cow as set forth in claim 1.

Sonication of the oocysts would result in a preparation containing both oocyst walls and sporozoites. Even if the initial sieving and sucrose density centrifugation step resulted in removal of some material from the outside wall of the oocysts (and there is no indication that this is the case), it is the sonicated oocyst preparation containing both oocyst and sporozoite material that is used to produce an immune response. Claim 9 requires that at least some of the oocyst wall is separated from the internal sporozoites to form an oocyst wall preparation. It is clear that this oocyst wall preparation does not contain sporozoites since they have been separated out. By contrast, an oocyst homogenate obtained by sonicating purified intact oocysts would contain sporozoites. Riggs *et al.* (1994) does not disclose nor teach a step where at least a portion of the oocyst wall is separated from the internal sporozoites with the resulting separated oocysts wall then being administered to an animal to produce antibodies.

The specification clearly states that the oocyst wall antigens should be separated from the sporozoite components (see page 4, lines 1-7), *i.e.*, sporozoite components should be removed from the preparation, because it appears that internal sporozoite antigens are more immunodominant. Riggs *et al.* (1994) does not disclose methods for obtaining purified oocyst wall preparations that lack sporozoites (page 13, line 33 to page 14, line 8) and therefore does not teach the removal sporozoite components as these components were administered to the animal in every case except the control where adjuvant only is administered. Consequently, this cited reference does not teach nor suggest the method of claim 9 nor dependent claims 10 to 15 and also does not enable the production of IgG1 class antibodies against oocyst wall antigens as set forth in claims 18 and 19.

Applicants respectfully request withdrawal of the obviousness rejection because neither McDonald *et al.* (1995) nor Riggs *et al.* (1994) discuss or suggest the problem of obtaining IgG1 class antibodies against oocyst wall antigens as set forth in Applicants' claims nor do these

references teach or suggest methodology, either separately or in combination, which would allow the skilled person to arrive at the claimed invention.

Conclusion

In view of the foregoing, Applicants respectfully request reconsideration and the timely allowance of the pending claims. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact Applicant's undersigned representative to expedite prosecution. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for in the attached petition, such an extension is requested and the fee should also be charged to our Deposit Account No. 50-0310.

Respectfully submitted
Morgan, Lewis & Bockius LLP

Dated: **October 25, 2001**
Morgan, Lewis & Bockius LLP
Customer No. **009629**
1800 M Street, N.W.
Washington, D.C. 20036
202-467-7000

Elizabeth C. Weimar
Registration No. 44,478

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 4 has been amended as follows:

4. (Twice Amended) The method according to claim 3 wherein the pretreating comprises boiling the oocysts in the presence of SDS [~~for a sufficient time~~] to generate the oocyst antigen preparation.

Claim 5 has been amended as follows:

5. (Twice Amended) The method according to claim 4 wherein the boiling of the oocysts is [~~continued~~] for at least one hour in the presence of 0.5% (w/v) SDS.